



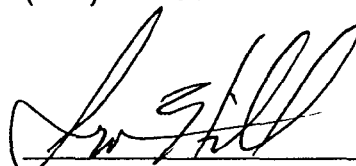
CLINICAL RESEARCH PROTOCOL WHOTI G-040

TITLE: Effect of Frequent Daily Use for Four Weeks of a MICRODENT® -  
containing, Sorbitol-based, Chewing Gum in Reducing Dental Plaque  
Accumulation When Compared to a Placebo Gum and A No-Chewing  
Control Period: A Double Blind, Crossover, Treatment Design

CONDUCTED BY: Dr. Thomas Schiff, D. M. D.  
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 5/8/98  
\_\_\_\_\_  
Signature of Responsible Party/Date

SPONSOR: Ira Hill, PhD  
WhiteHill Oral Technologies, Inc.  
950 Highway 36  
Hazlet, NJ 07730  
(201) 264-0044

 5/11/98  
\_\_\_\_\_  
Signature of Responsible Party/Date

A. TITLE: Effect of Frequent Daily Use for Four Weeks of a MICRODENT® containing, Sorbitol-based, Chewing Gum in Reducing Dental Plaque Accumulation When Compared to a Placebo Gum and A No-Chewing Control Period:  
A Double Blind, Crossover, Treatment Design

B. STUDY PRINCIPAL INVESTIGATOR: Thomas Schiff, D. M. D.

SPONSOR: Ira Hill, PhD  
WhiteHill Oral Technologies, Inc.

C. STATEMENT OF PURPOSE:

The purpose of this clinical trial is to compare in normal human subjects the effect on dental plaque accumulation, with normal brushing, by multiple daily use of a sorbitol-based, sugar-free chewing gum vs. a placebo chewing gum without the active ingredient (trademarked Microdent™<sup>(1)</sup>, a proprietary melt-emulsion of dimethicone\* in a suitable poloxamer<sup>(2)</sup> which acts as an agent to both clean and modify the tooth surface free energy) . It is an additional purpose to compare plaque accumulation during the use of both the test gum and the placebo gum by the same subjects with an equivalent period wherein no gum is chewed by those same subjects.

(1) Established as Category I for Safety (Generally Regarded As Safe) by the FDA Subcommittee for Plaque and Gingivitis Ingredient Review

(2) FDA reviewed Oral Care/Ingestible ingredients.

D. REVIEW OF THE LITERATURE:

1. General Overview of Plaque Formation and Effects, L. Menaker, Biologic Basis of Dental Caries, Chap. 5, 11, 12, 14, 16, 18., Harper and Row (1980)

2. Effect of Silicone (simethicone) on Alteration of Tooth Surface Energy and Plaque Attachment, Glanz (1969) and Baier and Glanz (1978))

3. Effect of silicone oil on protein adsorption to hydroxyapatite *in vitro* and on pellicle formation *in vivo*, M. Rykke and G. Rolla, *Scand J Dent Res*, 1990: **98**: 401-11.

4. Relevant Patents:  
U.S. Patent 4,950,479 "Method of Interrupting the Formation of Plaque"  
(24 literature citations, 31 patent references)

U.S. Patent 4,911,92 "Method and Apparatus for Adding Chemotherapeutic Agents to Dental Floss"

## E. EXPERIMENTAL DESIGN AND METHODS

### 1. Subject Selection

To participate in this clinical study, adults 18-65 years of age must meet the following criteria:

- a. Excluding third molars, each subject must have at least 20 natural teeth present in the mouth.
- b. Have no history of medications that are likely to effect gingival health, i.e. acute hormonal therapy, antialagogs, calcium channel blockers use as anti hypertension agents, anti-epileptic drugs, and steroids. The use of prophylactic antibiotics or antibiotic usage during the month preceding the study will be grounds for exclusion.
- c. No medical history of rheumatic fever, AIDS, leukemia, cirrhosis, sarcoidosis, diabetes melitis, hepatitis, current pregnancy or any physical condition that limits manual dexterity.
- d. A dental history that includes brushing the teeth at least once a day. Other reasons for exclusion are the presence of gross dental caries; gross neglect of oral hygiene; and the presence of advanced periodontitis, based on a non-invasive examination.
- e. No orthodontic appliances or removable prosthesis.
- f. Should not require premedication with antibiotics for dental appointments, including mitral valve clicks prolapse or other heart murmurs, heart valve replacement and artificial joint.
- g. Sign a consent form.
- h. At time of screening examination, the subject must have a Plaque Index score of at least 1.8 units (average of all surfaces scored). See Appendix A for criteria.

### 2. Screening Examination

After review of the subject's medical and dental history, the subject will be examined for a Plaque Index score of 1.8 units, or greater, (Turesky modification, 1970 of the Quigley-Hein criteria) using a disclosing solution.

### 3. Experimental Design

20 or more subjects will be selected from screening to assure at least 9 subjects/group at completion. This study will use a sequential treatment design wherein the same subjects will be evaluated before and after using each of the products over the specified time periods. The treatments will be four weeks in duration. The use of the "no-active" mint as a control period between crossover test periods for the gums will also serve as the "wash-out" period for the active.

A prior series of "range-finding" clinical trials (WHLS-003/004) and a full cross-over design clinical trial (WHLS-005) conducted at Univ. of the Pacific School of Dentistry, established that in a non-brushing protocol with a 48-hour use period and several formula variants of selected **test products** of sugar-free mints and chewing gums demonstrated a reduction in plaque accumulation ranging from about 8% up to 30% vs. the **placebo**. Several of the test products were statistically significant with only 10 subjects in the cross-over design. This design was especially useful for evaluating formula variables *in vivo*.

Plaque accumulation scoring will be performed by only one examiner (The Principle Investigator) throughout the study on a blind basis.

Assessment of plaque accumulation will be made at a baseline examination at the beginning of the study. Each subject will then be given a supragingival, rubber-cup prophylaxis to bring the starting plaque score to zero and product for use over the next four weeks distributed with instructions as follows:

Gum Chewing: Chew two pieces for 20- minutes three times a day. Times specified are "after meals or if a regular meal is not taken, then at the approximate time it would have been taken.

Mint Use: Dissolve one mint slowing in the mouth three times a day. Times specified are "after meals or if a regular meal is not taken, then at the approximate time it would have been taken.

At the end of each four week, with brushing, product-use period for each subject the plaque scores will be assessed for the "final" reading on that period's product. Baseline and all final examinations will be performed within the same one-hour time period of the respective day.

4. Protocol

Patients will be instructed to brush their teeth according to their normal oral hygiene patterns, using their regular brush and toothpaste except subjects will be screened and rejected for prior use of antimicrobial toothpastes such as Total®. They will be instructed to not use any mouth rinses. They will be instructed to use only those gums or mints provided at the times specified.

**SCHEDULE**

**Day 1**

Subjects have refrained from brushing 12 hours before Baseline Scoring.

**BASELINE EXAMINATION**

Perform a standard rubber cup prophylaxis to reduce initial plaque index to zero.

**PROPHY**

Subjects are divided into two groups and assigned either the placebo or test gum for the first leg of the crossover design.

Subjects are given coded packets containing sufficient quantities of the appropriate product for the full test period and instructed as to use.

Subjects are instructed concerning product use and specified restrictions on normal oral hygiene

**Day 28** (end of first leg of gum crossover)

Subjects have used specified product with normal oral hygiene since Day 1.

**FINAL EXAMINATION I**

Perform a standard rubber cup prophylaxis to reduce initial plaque index to zero.

**PROPHY**

All Subjects are given packets of a commercial, sorbitol-containing breathmint for sufficient quantity for the specified use during the no chewing gum control period and instructed as to mint use and frequency.

**Day 56** (end of no chewing gum control period)

Subjects have used specified mints with normal oral hygiene since Day 28.

FINAL EXAMINATION II

Perform a standard rubber cup prophylaxis to reduce initial plaque index to zero.

PROPHY

Subjects are assigned the gum not used from Day 1- 28, either the placebo or test gum, for the final leg of the crossover design.

Subjects are given coded packets containing sufficient quantities of the appropriate product for the full test period and instructed as to use.

Subjects are instructed concerning product use and specified restrictions on normal oral hygiene

**Day 84** (end of second crossover gum period)

Subjects have used specified product with normal oral hygiene since Day 56.

FINAL EXAMINATION III

Subjects instructed to return to normal habits for use of mints, gums or other oral hygiene products.

**TIMES OF USE**

1. After breakfast (if no meal taken then by 9 a.m. each day)
2. After lunch (if no meal taken then between 12 noon and 1 p.m.)
3. After dinner (if no meal taken then between 7 and 8 p.m.)

Compliance will not be monitored, but patients will be instructed to return all used product packets.

The clinical coordinator will provide each subject with appropriate product packages marked with the appropriate code. The Sponsor is responsible for breaking the code. Returned product will be examined only if final examination data presents anomalies which might be explained by examining returns.

5. Subject Protection/Liability

Since the procedures to which subject volunteers will be exposed are no different from those ordinarily used by each clinical site in routine evaluation and treatment of patients, the patient protection measures ordinarily employed by each clinical site with respect to prospective and accepted patients are sufficient. Informed consent of each subject accepted into the study will be recorded on a form customarily used by that clinical site and acceptable to its I.R.B. (See Appendix E-H). This will be included in the subject's clinical file along with his/her medical history form and data collected in the course of the study. Patients will be remunerated as deemed appropriate by the clinical site.

6. Principal Investigator's Duties

The Principal Investigator shall manage the study at his site to provide for proper blinding, orderly and professionally responsible handling of subjects and tests or examinations, accurate compilation of data, timely and accurate reporting to the Sponsor, and protection of Subjects' rights.

7. Monitoring

Employees, consultants, or other appropriately qualified agents of the Sponsor shall monitor the activities at each clinical site to assure adherence to the protocol and protection of subjects' rights.

8. Data Analysis

Appropriate statistical methods will be employed by the Sponsor to evaluate correlations among the parameters of the study. At minimum, correlations between plaque accumulation means will be determined. Comparisons will be made between the means of final examinations after the use of **placebo gum, control mints** and **test gum (with MICRODENT®)** product groups respectively. Correlation with incoming **baseline** means will be made to assure relevancy of test group data. Other exploratory analyses, both parametric and non-parametric may be employed.



## APPENDIX A

### Turesky Modification of Quigley Hein Plaque Scoring Method

- |   |   |  |
|---|---|--|
| 0 | = | No plaque.   |
| 1 | = | Separate flecks of plaque at the cervical margin of the tooth.                                 |
| 2 | = | A thin continuous band of plaque (up to one mm) at the cervical margin of the tooth.           |
| 3 | = | A band of plaque wider than one mm but covering less than one-third of the Crown of the tooth. |
| 4 | = | Plaque covering at least one-third but less than two-thirds of the crown of the tooth.         |
| 5 | = | Plaque covering two-thirds or more of the crown of the tooth.                                  |

1. Quigley GH & Hein JW JADA 65:26, 1962
2. Turesky, S. et. al. J. Periodont 41:41, 1970

If fleck of plaque (line angles or anywhere) is NOT in contact with gingiva - score it ZERO.

If it CONTACTS gingiva - same fleck is scored 1.

If 1 mm or less band but with small break - Score 2.

If any portion of band has area of more than 1 mm and/or less than 1 mm although it is not a continuous band (see illustration below) - score it 3.

APPENDIX B

STUDY QUESTIONNAIRE

PLEASE PRINT

Name \_\_\_\_\_

Telephone(Office) \_\_\_\_\_ (Home) \_\_\_\_\_

Office/Lab Address: \_\_\_\_\_ (Room) \_\_\_\_\_

Social Security # \_\_\_\_\_

Home Address: (Street) \_\_\_\_\_

(City) \_\_\_\_\_

(State & ZIP) \_\_\_\_\_

Gender (sex) \_\_\_\_\_

Age \_\_\_\_\_

Race \_\_\_\_\_

How many times per day do you brush? \_\_\_\_\_

Have you ever had a heart murmur? Yes \_\_\_\_\_ No \_\_\_\_\_

Have you ever had hepatitis? Yes \_\_\_\_\_ No \_\_\_\_\_

Do you have diabetes? Yes \_\_\_\_\_ No \_\_\_\_\_

Are you currently pregnant? Yes \_\_\_\_\_ No \_\_\_\_\_

## APPENDIX C

### University of the Pacific School of Dentistry Informed Consent - Chewing Gum & BreathMint Study

If accepted for this study, you will participate in a three month investigation of the efficacy of a series of chewing gums and breathmints on reducing plaque accumulation with your normal tooth brushing habits. The breathmints and chewing gums contain only ingredients that are commercially available and FDA approved. You are asked to participate because you are an apparently health adult with most of your natural teeth. You must come for a total of four examinations - at the beginning and at the end of three one month product use periods. A tooth cleaning will be performed just after the each of the first three examinations. The teeth and gums will be examined and a removable stain to disclose plaque (germs) will be applied to the teeth. It is estimated each examination will require 10-15 minutes. You will use the breathmints or chewing gum in a normal fashion 3 times a day during the test period. At the conclusion of each four week segment of the study you will be paid \$150, provided you miss no appointments **and return all the unused breathmints/gums and packets at the end of the study.**

Assignment of products the first and third months will be made on a random basis. During the second month, all subjects will use a specified breathmint. During the study, you will brush as you have always done but you cannot use an antimicrobial toothpaste, a therapeutic mouthrinse or gums and mints other than those provided. Routine dental treatment, other than cleanings, may be done during the three months of the study. You should report to us any antibiotics or other prescription drugs taken during the study.

Your decision not to participate in the study or to withdraw after the study starts will not prejudice your future relations with the University of the Pacific School of Dentistry.

Your signature below indicates that you understand that UOP has made no provision for monetary compensation to you in the event of physical injury resulting from the research procedures. Should physical injury occur, medical treatment is available, but treatment is not provided free of charge.

If you have any question, we expect you to ask us. If you have additional questions later, Dr. Schiff can be reached at the Department of Radiology, University of the Pacific School of Dentistry.

You are making a decision whether or not to participate. Your signature indicates you have decided to participate after having read the information above.

Signature\_\_\_\_\_ Date\_\_\_\_\_

Signature of Investigator\_\_\_\_\_

APPENDIX E

RESEARCH AGREEMENT

Between

WHITEHILL ORAL TECHNOLOGIES, INC.

And

UNIVERSITY OF THE PACIFIC SCHOOL OF DENTISTRY

THIS RESEARCH AGREEMENT, made this day, by and between WhiteHill Oral Technologies, Inc. (hereinafter referred to as "the Sponsor") and the University of the Pacific School of Dentistry (hereinafter referred to as "the University").

NOW THEREFORE, THE PARTIES HERETO AGREE AS FOLLOWS:

ARTICLE I: STATEMENT OF WORK. The University agrees to use its best efforts to perform the research program entitled "Effect of Frequent Daily Use for Four Weeks of a Microdent™ containing, Sorbitol-based, Chewing Gum in Reducing Dental Plaque Accumulation When Compared to a Placebo Gum and A No-Chewing Control Period."

ARTICLE II: PRINCIPAL INVESTIGATOR. The research will be supervised by Dr. Thomas Schiff. If, for any reason, Dr. Schiff is unable to serve as Principal Investigator, and a successor acceptable to both the University and the Sponsor is not available, this Agreement shall be terminated as provided in Article VI.

ARTICLE III: PERIOD OF PERFORMANCE. The performance of this Agreement shall begin May 15, 1998, and shall not extend beyond the estimated completion date of August 15, 1998, unless the period is further extended by amendment to this Agreement. However, the University shall have no liability to Sponsor, nor shall it be in default under this agreement if performance is delayed or prevented by any cause beyond the University's control.

ARTICLE IV: REIMBURSEMENT OF COSTS. In consideration of the foregoing, the Sponsor will reimburse the University for all costs (direct and indirect) incurred in the performance of the research which shall not exceed the total estimated project cost of \$42,500 without written authorization from the Sponsor.

ARTICLE V: PAYMENT. Payments shall be made to the University by the Sponsor in advance on the following schedule:

1. \$20,000 payable by May 15, 1998; and
2. \$20,000 payable on delivery of top line data
3. Balance (\$2,500) payable after submission of final data sheets and conclusions by principle investigator.

ARTICLE VI: TERMINATION. Performance under this Agreement may be terminated by the Sponsor upon sixty (60) days written notice; performance may be terminated by the university if circumstances beyond its control preclude continuation of the research. Upon termination, the University will be reimbursed as specified in Article IV for all costs and non-cancelable commitments incurred in the performance of the research prior to the termination date of the Agreement. Such reimbursement is not to exceed the total estimated project cost specified in Article IV.

ARTICLE VII: PUBLICATIONS. The University will be free to publish papers dealing with the results of any research under this Agreement. Where appropriate the University will give a copy of the paper to the Sponsor at least thirty (30) days prior to the intended submission for publication to allow the Sponsor to review for patent purposes and/or for inadvertent disclosure of the Sponsor's proprietary data.

ARTICLE VII: SPONSOR PROPRIETARY DATA. The free dissemination of information is an essential and long-standing policy of the University. However, under exceptional circumstances, the University recognizes that it may properly hold in confidence data supplied by a sponsor which the University considers essential for the conduct of a research program. Accordingly, the University's acceptance and use of any proprietary data which may be supplied by the Sponsor in the course of this research project shall be subject to the following:

- (a) The data must be marked or designated in writing as proprietary to the Sponsor.
- (b) The University retains the right to refuse to accept any such data.
- (c) Where the University does accept such data as proprietary, it agrees to exercise all reasonable efforts not to publish or otherwise reveal the data to others without the permission of the Sponsor, unless the data has already been or is subsequently published or disclosed publicly by third parties, was previously known or subsequently independently discovered by the University without the benefit of the proprietary data, or is required to be disclosed by order of a court of law or other governmental authority. It is agreed that such reasonable efforts by the University or other governmental authority will be in lieu of all other obligation or liabilities of the University relative to proprietary

ARTICLE IX: PATENTS. Title to any invention or discovery made or conceived by University personnel in the performance of the research shall remain with the University provided, however, that the University shall grant to the Sponsor the rights of first negotiation to obtain a license to make, use, and/or sell such invention or discovery, with the right to sublicense, under reasonable terms. The terms of exclusivity, fees and royalty rates will be negotiated with the University at the time the invention or discovery is made, provided further, however, that this right must be exercised by the Sponsor by notice in writing to the University within three (3) months from the date the invention or discovery is first disclosed to the Sponsor.

If the University files patent applications or otherwise obtains patent rights which relate to the licensed products of this Agreement, and if the Sponsor shall obtain rights to a further option or a license under such patent rights as are set forth in this section, the Sponsor shall bear the reasonable costs for the preparation, filing and prosecuting of the patent applications under which the Sponsor accepts a license, but in no case beyond an appeal to and a decision by the United States Patent and Trademark Office Board of Appeals, unless the Sponsor specifically agrees otherwise in writing.

ARTICLE X: USE OF NAMES. Neither party will use the name of the other nor the name of any of its employees in any form of publicity without the written permission of the other. In the case of the University, permission of the University Relations Office is required.

ARTICLE XI: ASSIGNMENT. Neither this Agreement nor the rights herein granted to the University shall be assignable or otherwise transferrable by the University without the Sponsor's prior written consent, except that the University may assign or otherwise transfer this Agreement or the rights granted herein to a University-related, non-profit research foundation. Such assignment shall not relieve the University of its obligations hereunder and the Sponsor may ask for reasonable assurances to such effect. Any such assignee for the University shall be bound by the terms hereof as if such assignee were the original party hereto.

ARTICLE XII: INDEPENDENT CONTRACTOR. In the performance of this agreement the University shall be an independent contractor. Neither party is authorized to act as the agent for the other and neither shall be bound by the acts of the other.

ARTICLE XIV: APPLICABLE LAW. This agreement shall be governed by the laws of the State of California.

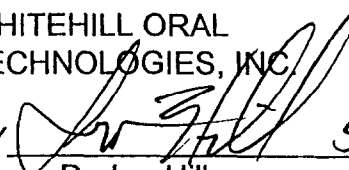
UNIVERSITY OF THE PACIFIC  
SCHOOL OF DENTISTRY

BY

  
Dr. Thomas Schiff (date) 5/6/98

WHITEHILL ORAL  
TECHNOLOGIES, INC.

BY

  
Dr. Ira Hill (date) 5/4/98